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International application number: PCT/US05/010005

International filing date: 23 March 2005 (23.03.2005)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/555,448
Filing date: 23 March 2004 (23.03.2004)

Date of receipt at the International Bureau: 13 June 2005 (13.06.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



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APPLICATION NUMBER: 60/555,448

FILING DATE: *March 23, 2004*

RELATED PCT APPLICATION NUMBER: *PCT/US05/10005*



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032304

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PTO/SB/16 (10-01)
Approved for use through 10/31/2002. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE**PROVISIONAL APPLICATION FOR PATENT COVER SHEET**

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No.

E193107628US

2264 U.S. PTO
60/555448

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INVENTOR(S)					
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)			
John, A. Baudouin Guilford	Porco Gerard Jones	Chestnut Hill, MA Allston, MA Canton, MA			
<input type="checkbox"/> Additional inventors are being named on the _____ separately numbered sheets attached hereto					
TITLE OF THE INVENTION (500 characters max)					
Synthesis of the Aglain Skeleton by Photogeneration and Dipolar Cycloaddition of Oxidopyryliums Derived from 3-Hydroxyflavanones					
Direct all correspondence to: CORRESPONDENCE ADDRESS					
<input checked="" type="checkbox"/> Customer Number		<div style="border: 1px solid black; padding: 2px;">022383</div> <small>Type Customer Number here</small>		Place Customer Number Bar Code Label here	
OR					
<input type="checkbox"/> Firm or Individual Name					
Address					
Address					
City		State		ZIP	
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ENCLOSED APPLICATION PARTS (check all that apply)					
<input checked="" type="checkbox"/> Specification		Number of Pages		<div style="border: 1px solid black; padding: 2px;">3</div>	
<input checked="" type="checkbox"/> Drawing(s)		Number of Sheets		<div style="border: 1px solid black; padding: 2px;">13</div>	
<input type="checkbox"/> Application Data Sheet. See 37 CFR 1.76		<input type="checkbox"/> CD(s), Number		<div style="border: 1px solid black; width: 80px; height: 20px;"></div>	
		<input type="checkbox"/> Other (specify)		<div style="border: 1px solid black; width: 150px; height: 20px;"></div>	
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT					
<input checked="" type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27.				<div style="border: 1px solid black; padding: 5px;">FILING FEE AMOUNT (\$) \$80.00</div>	
<input type="checkbox"/> A check or money order is enclosed to cover the filing fees					
<input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number:					
<input type="checkbox"/> Payment by credit card. Form PTO-2038 is attached.					
				<div style="border: 1px solid black; padding: 2px;">023255</div>	
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.					
<input checked="" type="checkbox"/> No.					
<input type="checkbox"/> Yes, the name of the U.S. Government agency and the Government contract number are: _____					

Respectfully submitted,

SIGNATURE

TYPED or PRINTED NAME John A. Porco, Jr.

TELEPHONE (617) 353-2493

Date 03/23/2004

REGISTRATION NO.

(if appropriate)

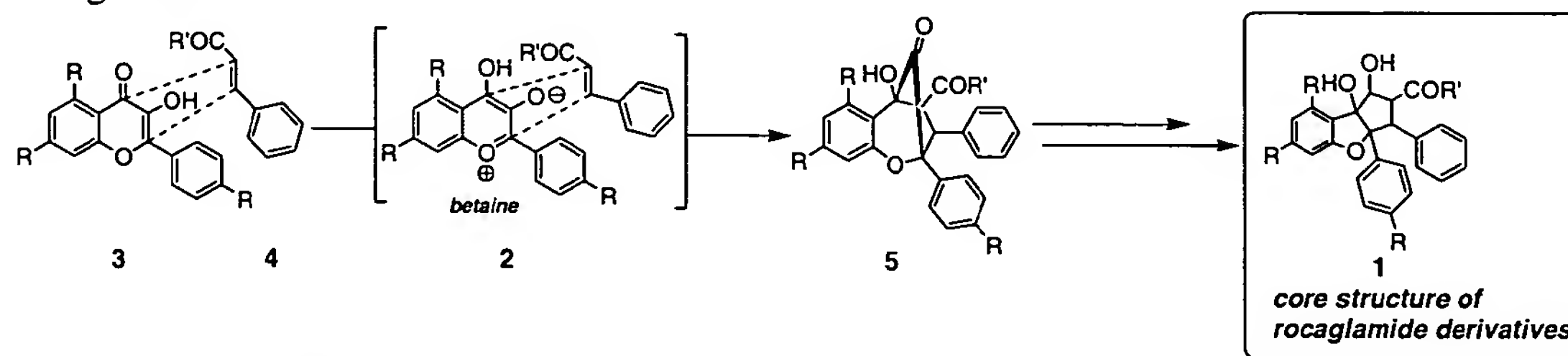
Docket Number:

BU04-17

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C. 20231.

Our laboratory has recently embarked on a synthetic chemistry project involving the synthesis of the core structure **1** of the rocaglamides and related antitumor natural products (**Scheme 1**). Our essential approach involves generation of the oxidopyrylium species **2** from a 3-hydroxyflavone derivative **3** and subsequent dipolar cycloaddition to cinnamate derivatives **4** to afford the aglain skeleton **5** and thence rocaglamide framework **1** after rearrangement of **5** and further modifications.



Scheme 1: Biomimetic approach of the rocaglamide core structure

Literature reports have documented excited state intramolecular proton transfer (ESIPT) of 3-hydroxyflavone (3-HF) derivatives leading to the formation of the requisite oxidopyrylium betaine-type dipoles **2**. The overall ESIPT process (**Figure 1**) involves generation of a putative tautomeric form of 3-HF where the proton of the hydroxyl group at C3 position migrates to the ketone group at C4 position to yield a oxidopyrylium species (tautomeric form **T**). Although ESIPT processes of 3-HF derivatives have been reported in the literature to produce excited state species such as **T**, to our knowledge there are no reports of chemical reactions *e.g.* cycloaddition processes with these potentially reactive intermediates.

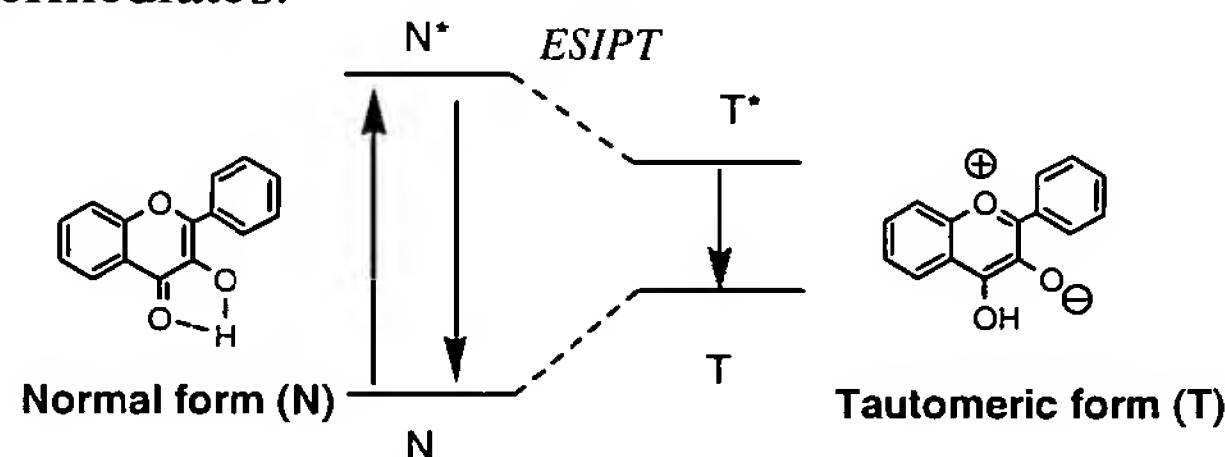


Figure 1: ESIPT and fluorescence emission in 3HF

Our initial efforts toward understanding the cycloaddition reactivity of the oxidopyrylium species **T** was focused on model studies with commercially available 3-hydroxyflavone (**Figure 2**). Photoirradiation of **6** in the presence of the dipolarophile methyl cinnamate **7** (5 equivalents) in acetonitrile as solvent produced

a mixture of products (**Figure 2**). According to spectroscopic data (^1H NMR and IR) and X-ray analysis (**Figure 3**), the major compound produced in 56 % chemical yield was confirmed to be the [3+2] cycloadduct **8**.

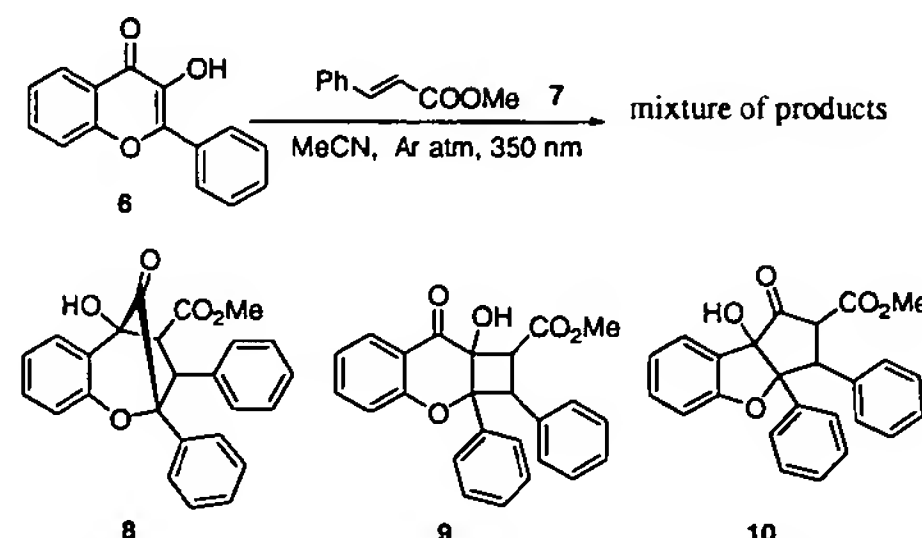


Figure 2: Possible cycloadducts obtained from the cycloaddition between 3HF and methyl cinnamoyl ester

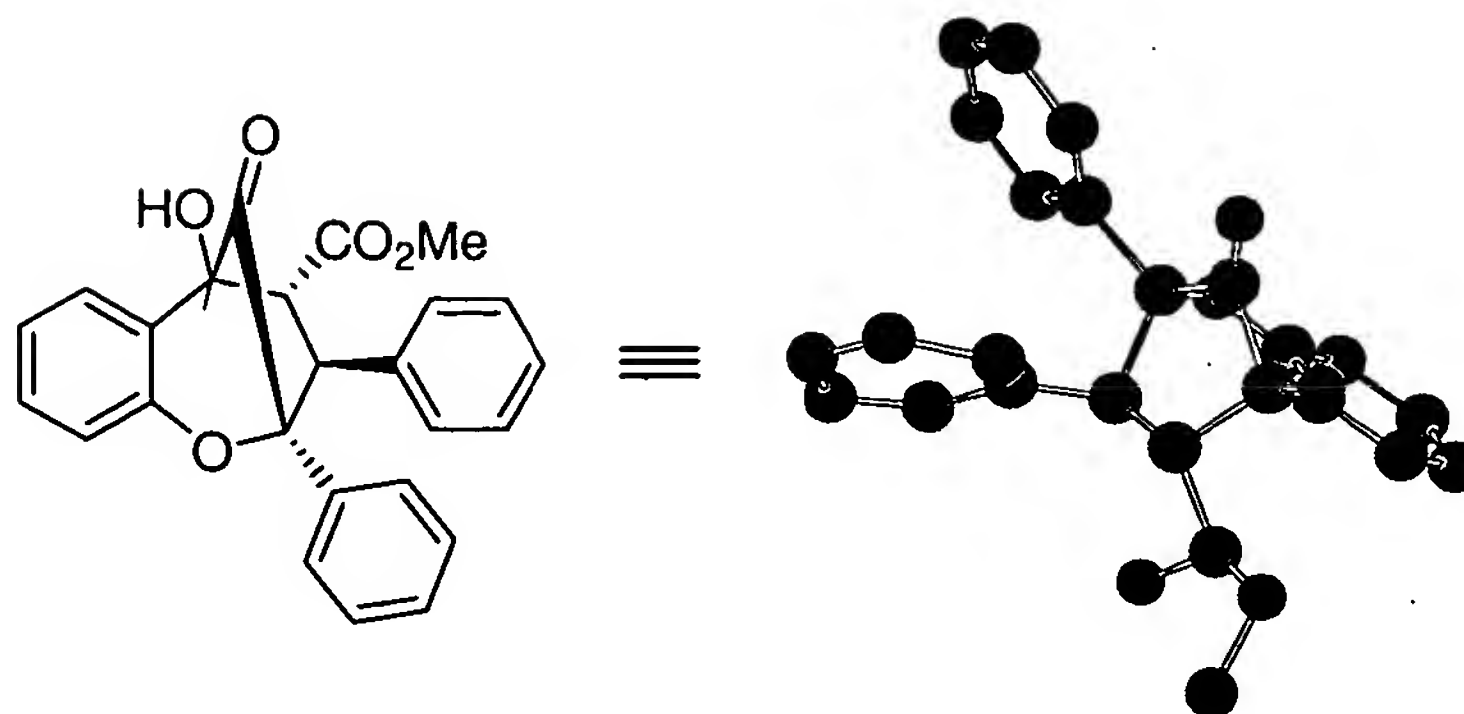
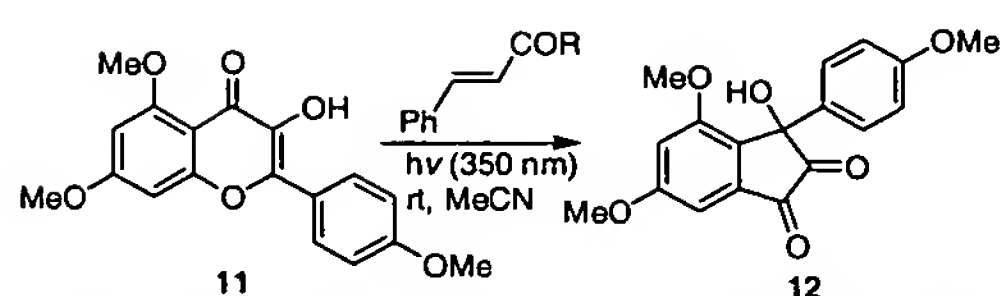


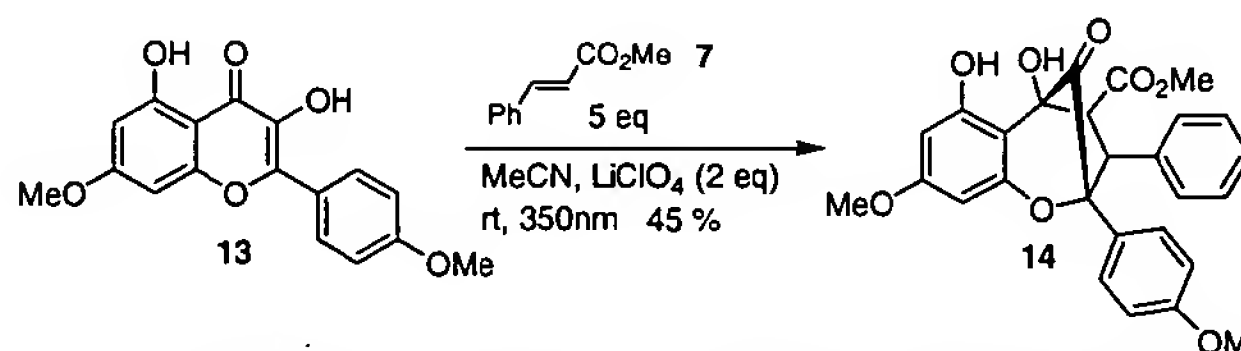
Figure 3: X-ray analysis of cycloadduct **8**



Scheme 2: Photolysis of trisubstituted 3HF

Attempted cycloaddition using **11** failed to yield any cycloaddition product but instead afforded the byproduct 3-aryl-3-hydroxy-1,2-indandione **12** (**Scheme 2**). In contrast, photoirradiation of the 5-OH derivative **13** at 350 nm (MeCN, rt) did not afford any

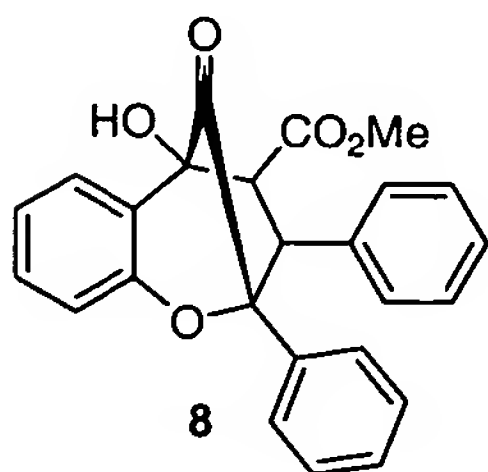
perceptible photorearrangement product. When **13** was photoirradiated in the presence of methyl cinnamate as dipolarophile, no cycloadduct was formed. However, initial experiments indicated that inclusion of different metal cations (*e.g.* LiClO₄, Zn (OTf)₂, and Y(OTf)₃) facilitated formation of cycloadduct **14** (proposed structure, regio- and stereoselectivity not known), **Scheme 4**. This indicates a specific potential requirement for both a 5-OH substituent and metal cation in order to potentially generate photochemically and react an oxidopyrylium from a 3-hydroxyflavanone such as **13**.



Scheme 4: possible cycloadduct obtained using Li(ClO₄)

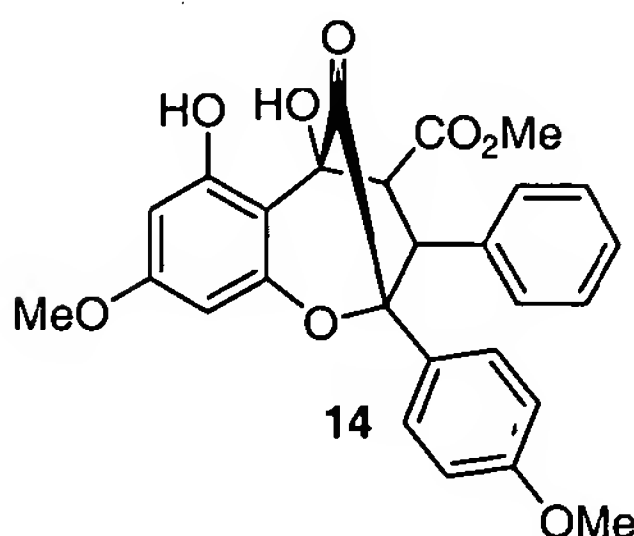
Summary: In preliminary experiments, we have found that the parent 3-hydroxyflavanone undergoes photoirradiation in the presence of a dipolarophile to produce an apparent cycloadduct resulting from 1,3 dipolar cycloaddition. However, in preliminary studies employing more highly oxygenated 3-hydroxyflavanone derivatives, we have found that it may be necessary to utilize a 5-hydroxy flavanone derivative in conjunction with a metal salt additive for the cycloaddition process to successfully occur.

Experimental procedure



General procedure for preparation of aglain derivative 8.

To a test tube (16 x 100 mm) was charged with commercially available 3-hydroxyflavone **6** (Indofine Chemical Company) (400 mg, 1.7 mmol) and methyl cinnamate **7** (650 mg, 4 mmol) and 8 mL of anhydrous acetonitrile. After degassing using Ar, the mixture was submitted to irradiation (350 nm, Hanovia UV lamp with uranium filter), at rt for 2 hours. The solution was concentrated *in vacuo* to afford a yellow oil. Purification *via* flash chromatography (60:40 hexanes/EtOAc) afforded 370 mg (0.94 mmol, 56 %) of aglain derivative **10** as a colorless solid. IR ν_{max} (film): 3452.43, 3060.19, 3033.01, 2939.81, 1766.99, 1735.92, 1607.77, 1584.47, 1483.50, 1452.43 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.34-76.82 (14 H, m), 4.631 (1 H, d, $J = 8.4$ Hz), 3.645 (1 H, d, $J = 8.4$ Hz), 3.606 (3 H, s), 3.57 (1 H, s); HRMS (CI/ NH_3) m/z calculated for $\text{C}_{25}\text{H}_{20}\text{O}_5$ 400.1311 found 401.1357 (M+H).



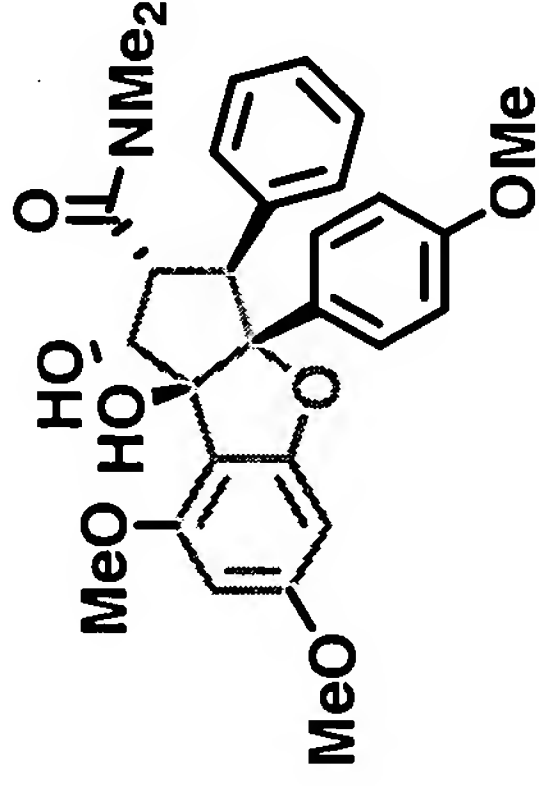
General procedure for preparation of aglain derivative 14.

To a test tube (16 x 100 mm) charged with 5-hydroxyflavonone **13** (20 mg, 0.064 mmol), methyl cinnamate **7** (155 mg, 0.92 mmol), and lithium perchlorate (13.5 mg, 0.12 mmol) was added 2 mL of anhydrous acetonitrile. After degassing using Ar, the mixture was submitted to irradiation (350 nm) at rt for 17 hours. The organic layer was washed once with 2 mL of water and 2 mL of saturated brine. After drying over MgSO_4 and concentrated *in vacuo* to afford a yellow oil. Purification *via* flash chromatography (60:40 hexanes/EtOAc) afforded 7 mg (0.015 mmol, 45 %) of aglain **14** as a yellow solid. IR ν_{max} (film): 3378.64, 2955.34, 2920.39, 2846.60, 1778.64, 1712.62, 1623.30, 1580.58, 1518.45, 1491.26, 1429.13, 1254.37, 1145.63 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.15 (1 H, s), 7.28 (2 H, d, $J = 9.2$ Hz), 7.04-7.00 (3 H, m), 6.80-6.78 (2 H, m), (6.635, 2d, $J = 9.2$ Hz), 6.06 (2H, m), 4.56 (2 H, d, $J = 8$ Hz), 4.31 (1 H, s), 3.72 (3H, s), 3.69 (3H, s), 3.67 (3H, s), 3.51 (2H, d, $J = 8$ Hz), HRMS (CI/ NH_3) m/z calculated for $\text{C}_{27}\text{H}_{24}\text{O}_8$ 476.1471 found 476.9583.

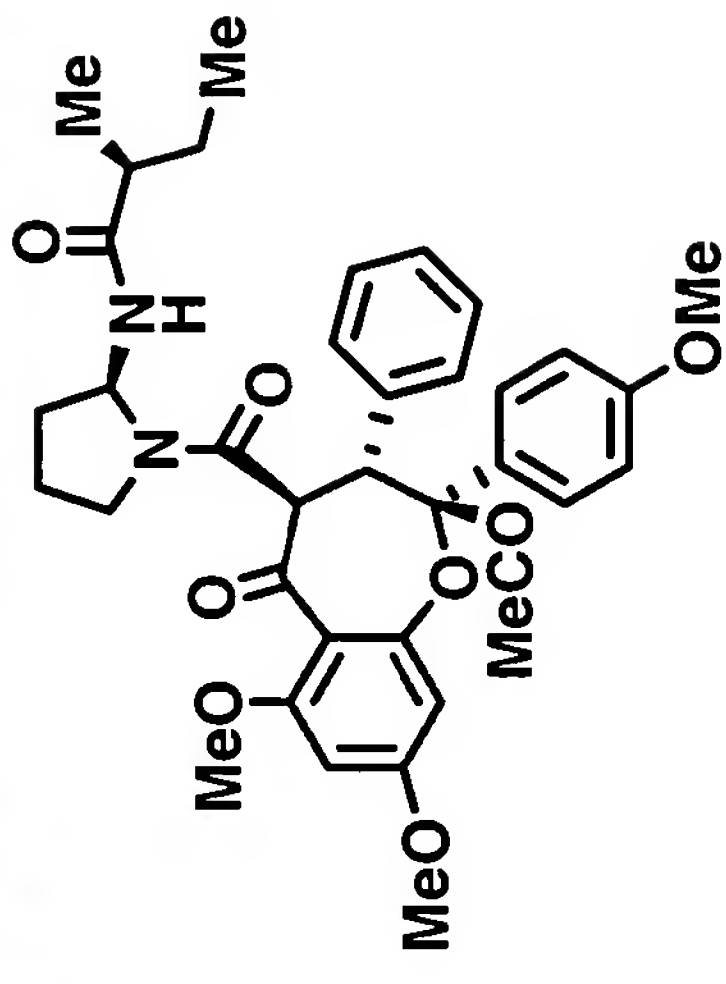
I) Background and significance

A) Origin and biological activities

Rocaglamide derivatives



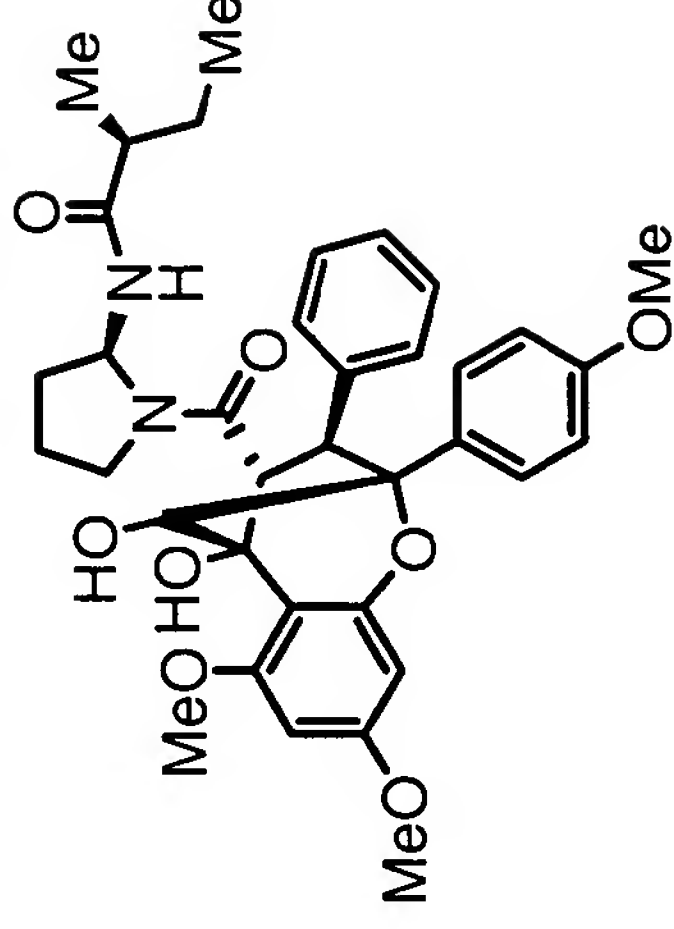
Forbaglin derivatives



Biological activities:

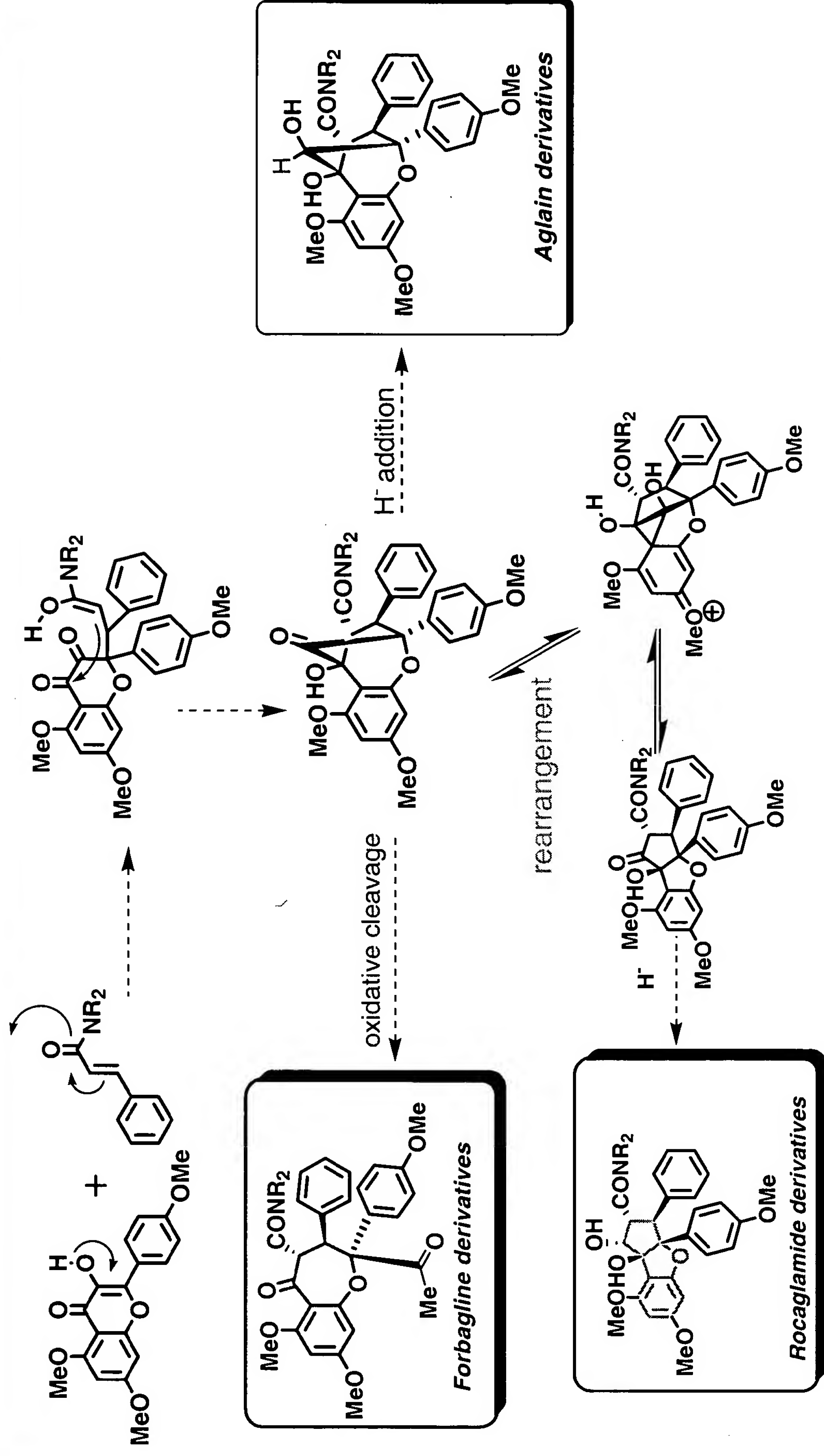
- Anti-inflammatory
- Insecticide
- Cytostatic activities against human cancer cell lines

Aglain derivatives



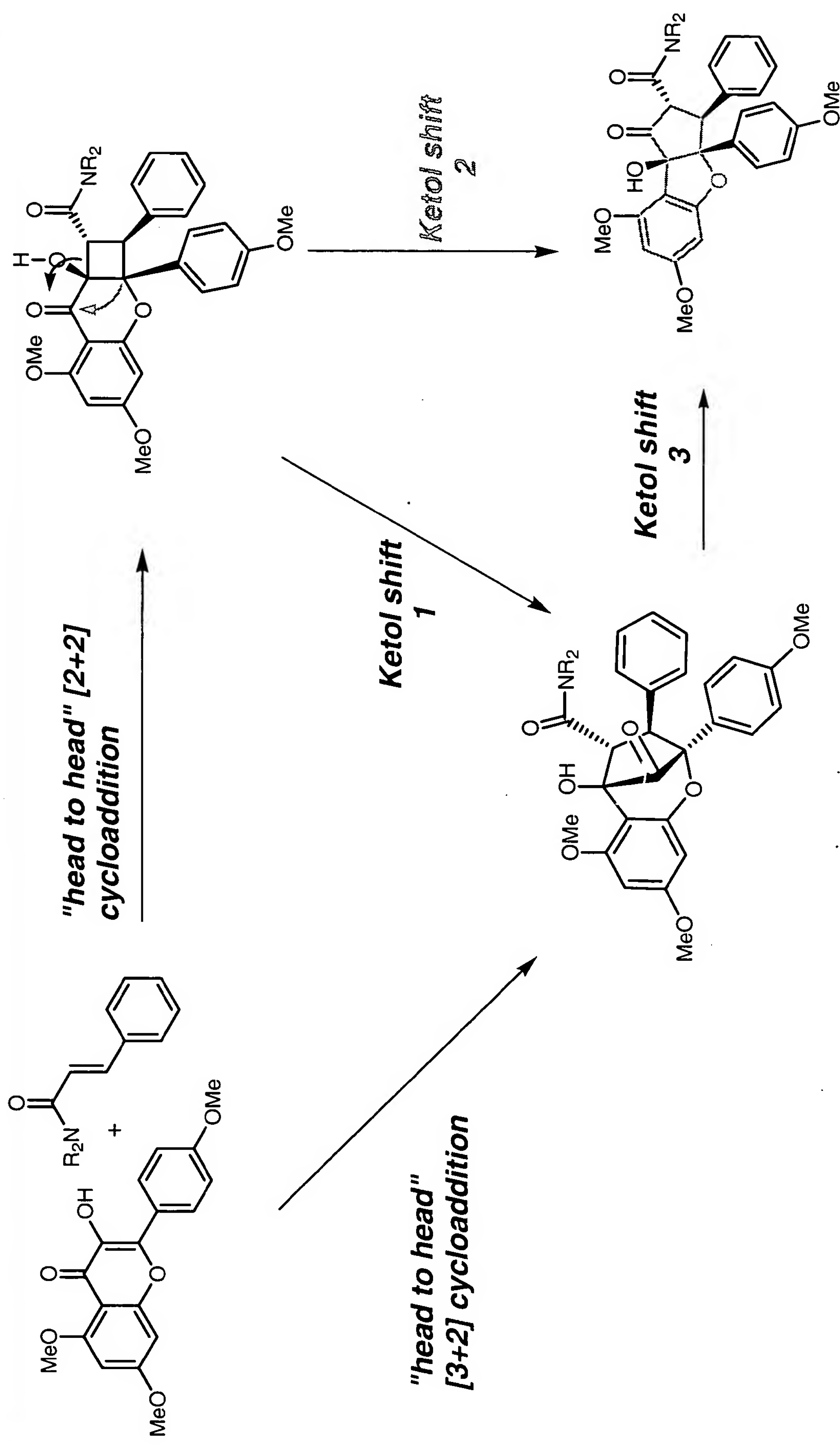
I) Background and significance

B) Proposed biosynthesis of rocaglamide derivatives (Proksch)



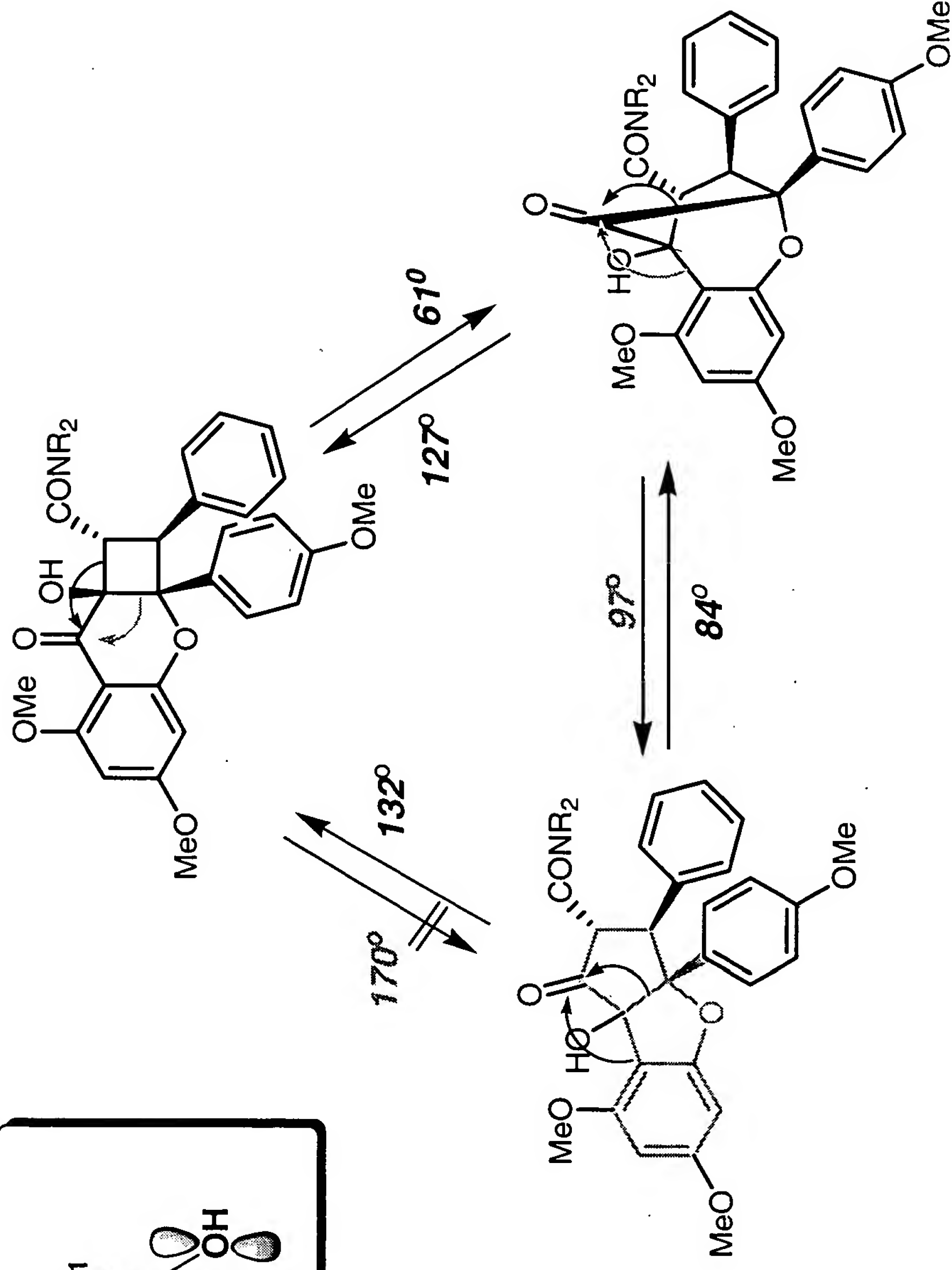
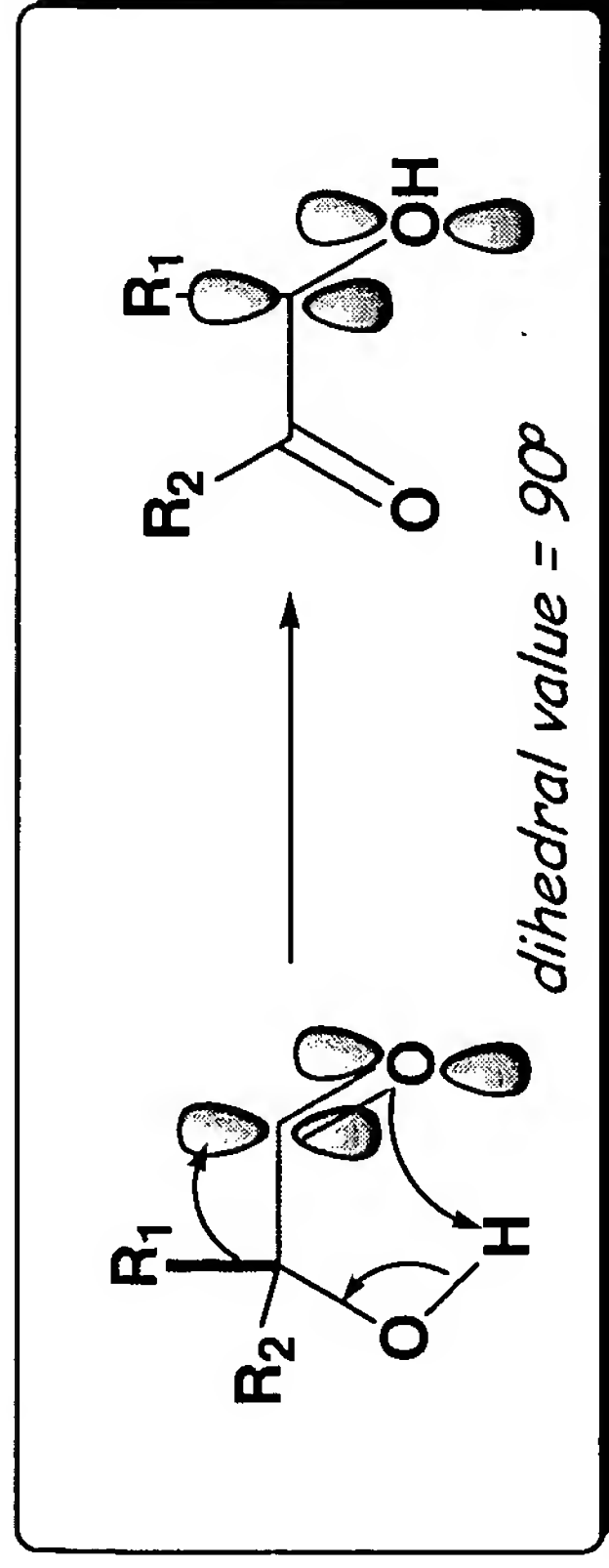
II) Proposed biomimetic synthesis

A) Biomimetic synthesis of rocaglamide derivatives based on [2+2] and [3+2] cycloaddition (Porco group)



II) Proposed biomimetic synthesis

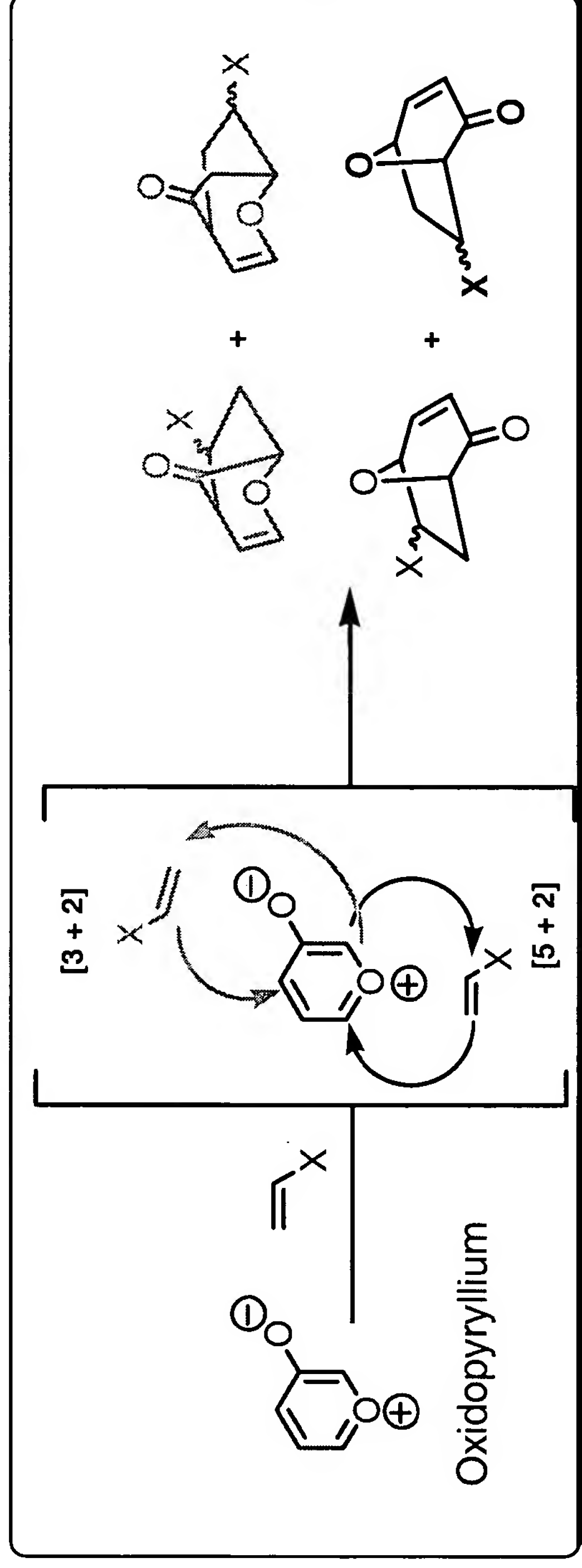
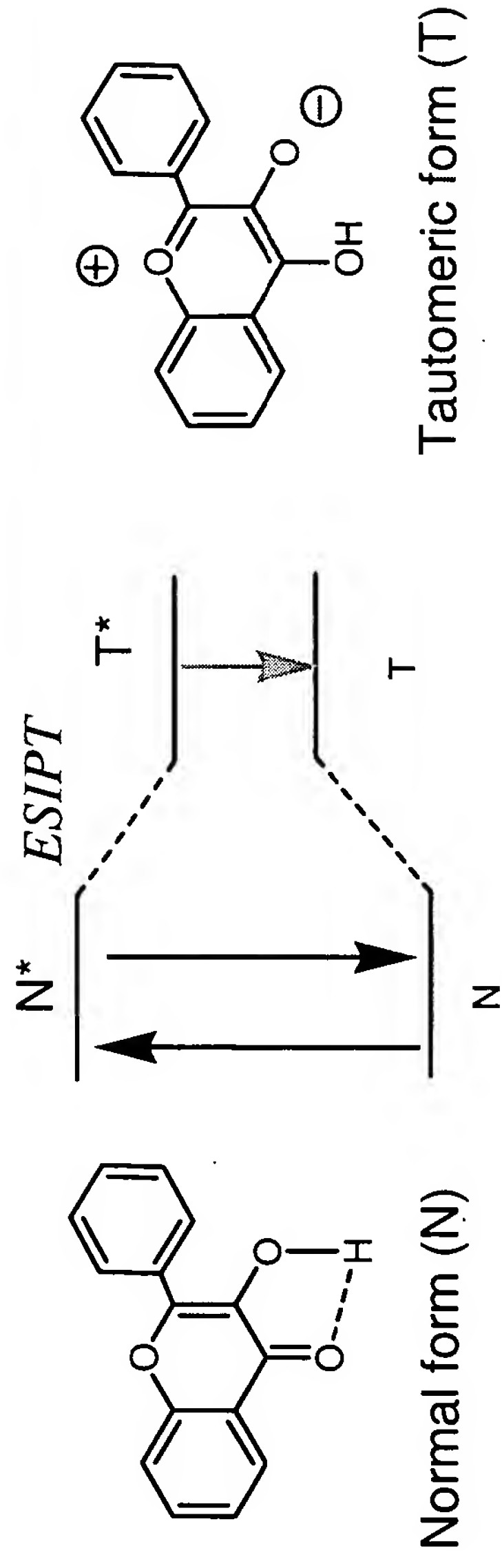
B) Ketol shift equilibrium between the different ring systems



Dihedral angle values has been obtained after energy minimization of the different ring system using molecular mechanics (PC Spartan)

II) Our Proposed biomimetic synthesis

C) Excited State Intramolecular Proton Transfer (ESIPT)

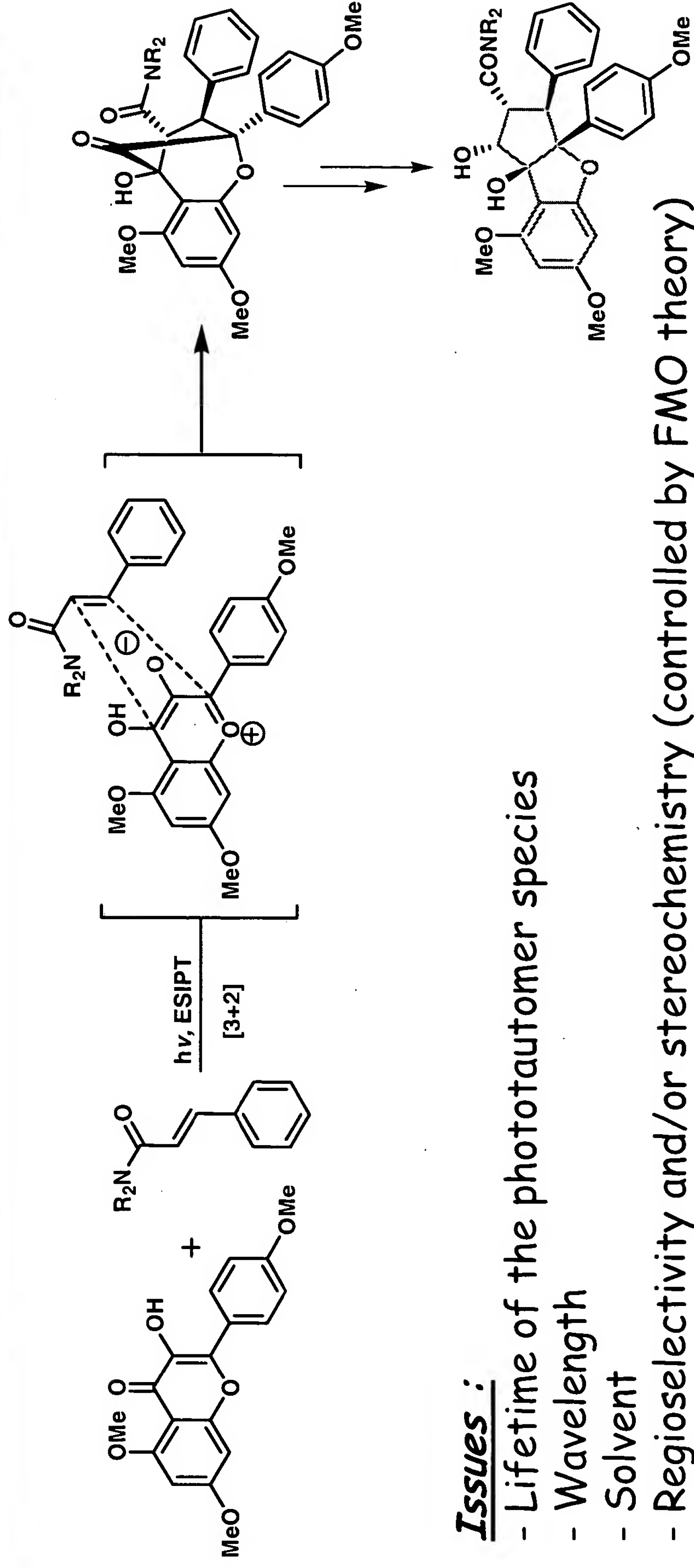


Excited State Intramolecular Proton Transfer of 3-hydroxyflavones :

(a) Samanta, A.; Mandal, P. K.; *J. Phys. Chem. A*, **2003**, *107*, 6334-6339. (b) Demchenko, A. P. *J. Phys. Chem. A*, **2003**, *107*, 4211-4216. (c) Rastogi, R.; Sharma, N.; Jain, S. K.; *Spectrochem Acta, Part A*, **2001**, *57*, 299-308

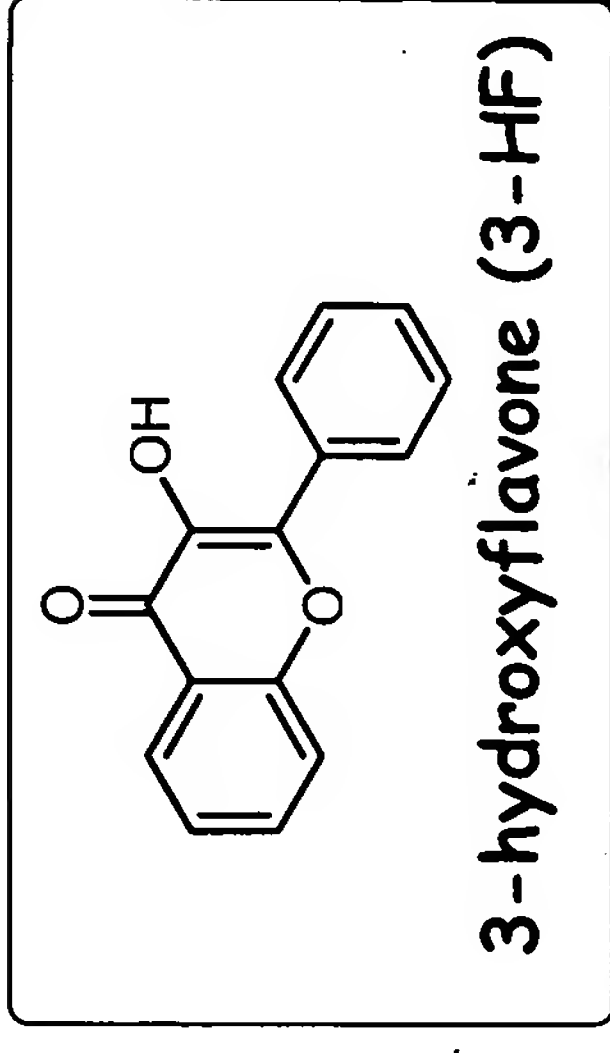
II) Proposed biomimetic synthesis

C) [3+2] cyclization



Issues :

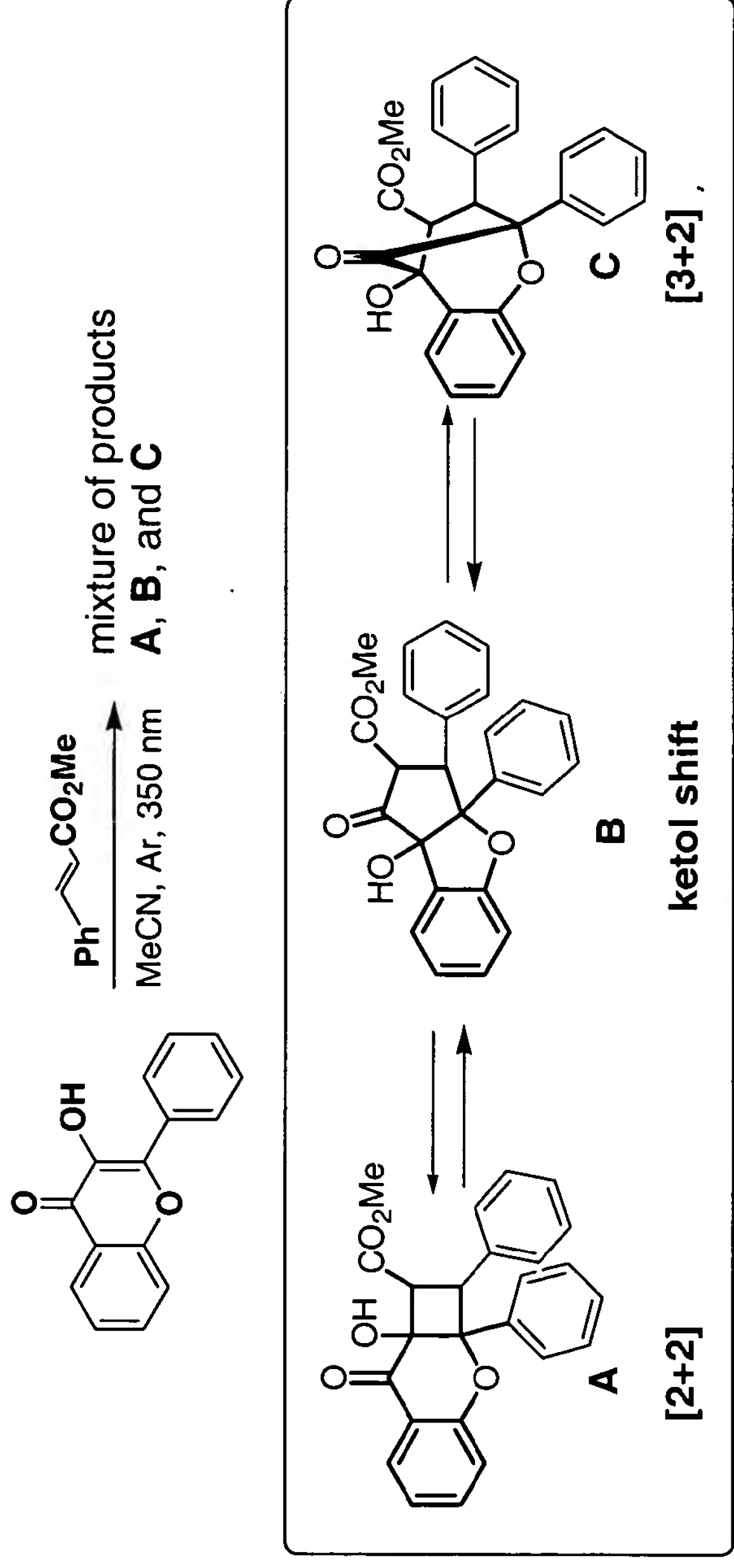
- Lifetime of the phototautomer species
- Wavelength
- Solvent
- Regioselectivity and/or stereochemistry (controlled by FMO theory)



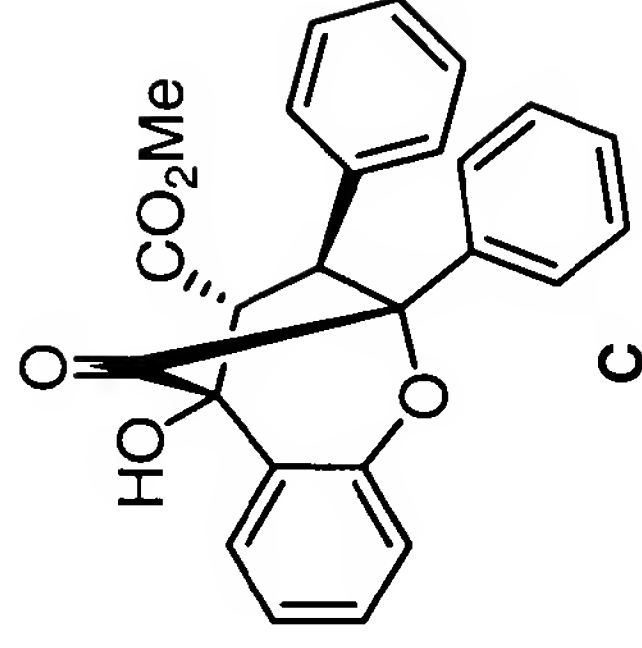
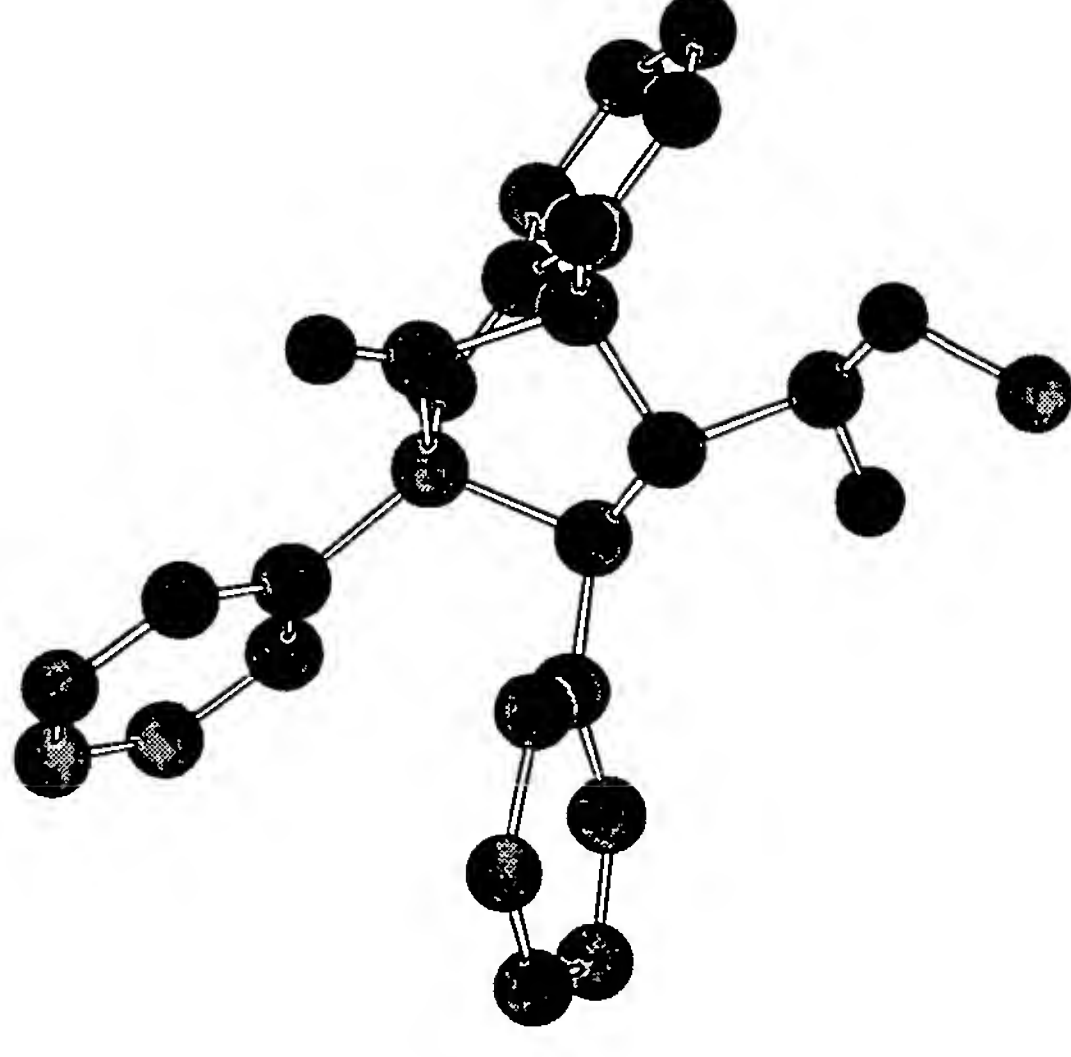
⇒ We began our study with 3-HF as a model system

III) Preliminary result

A) Model study : 3-hydroxyflavone (3HF)

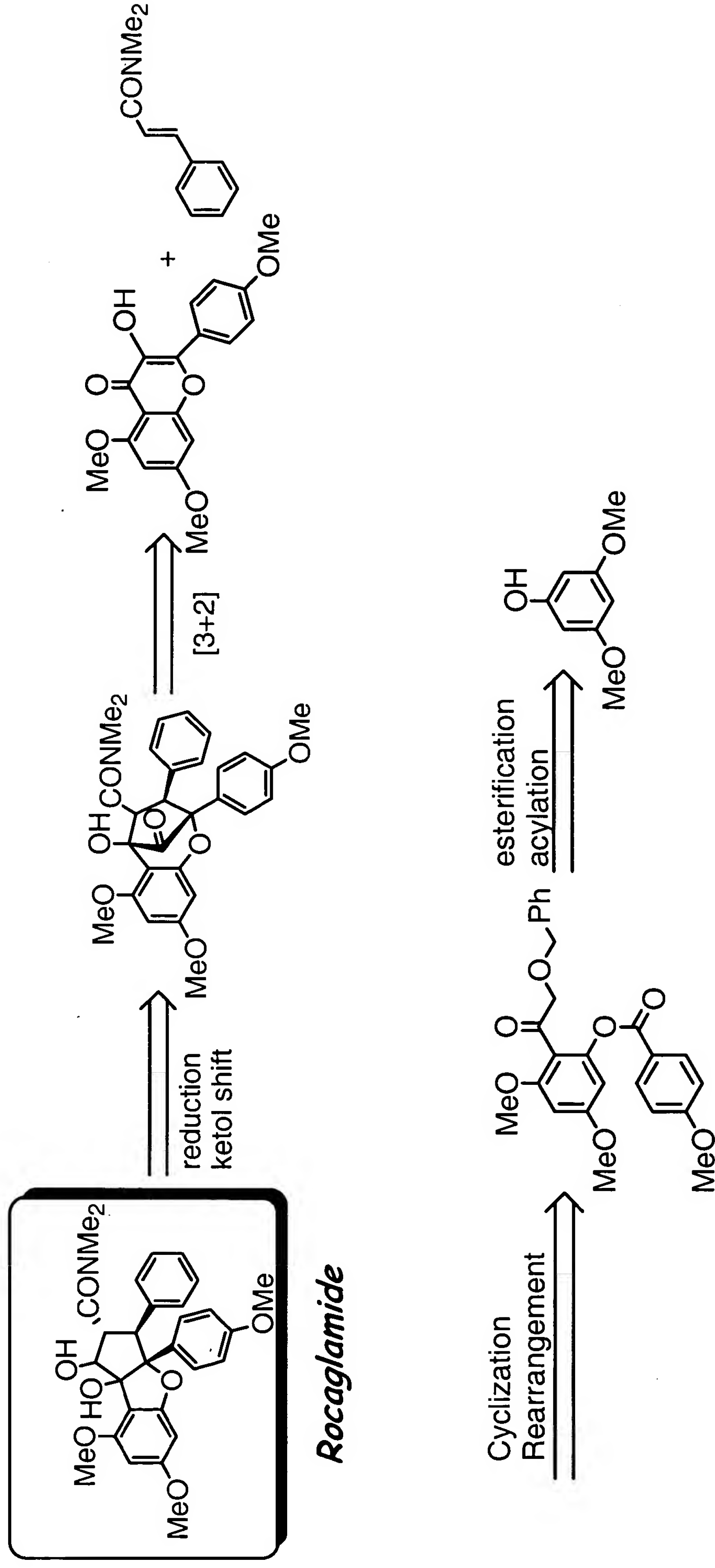


X ray analysis



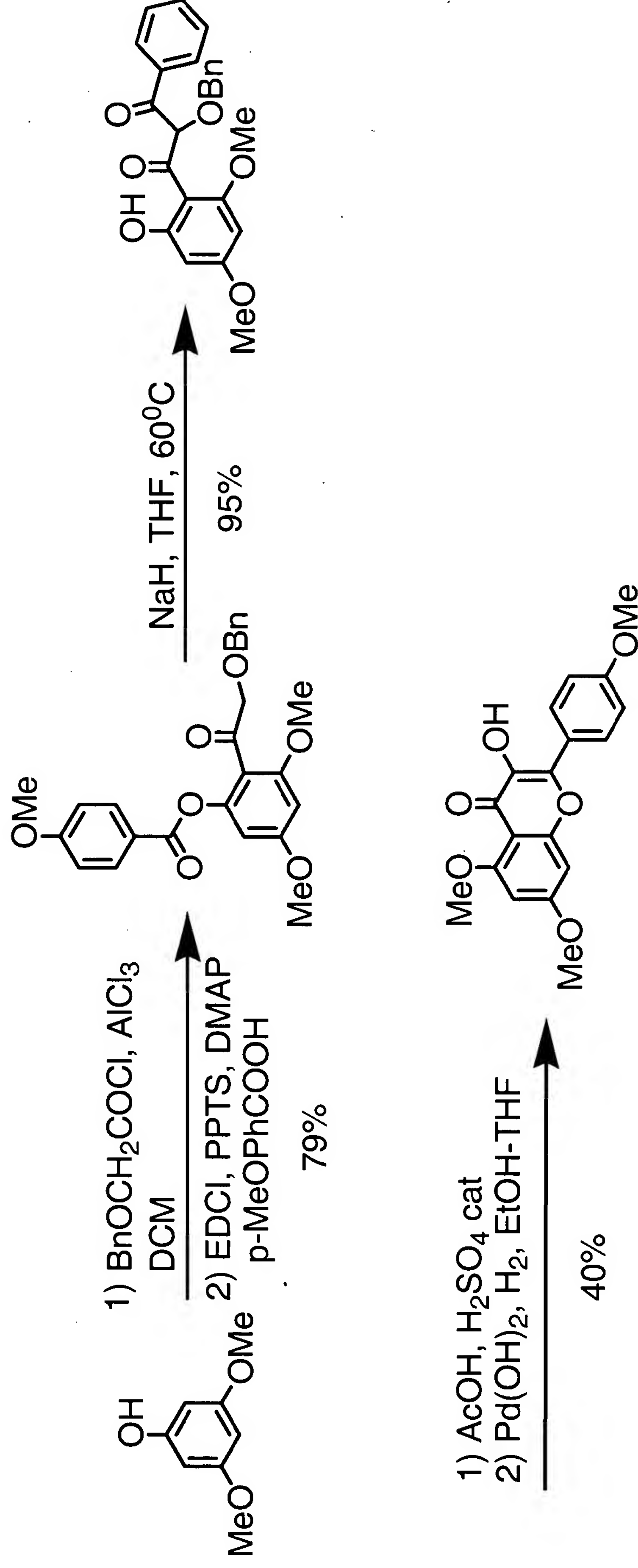
III) Preliminary result

B) Retrosynthesis of rocaglamide



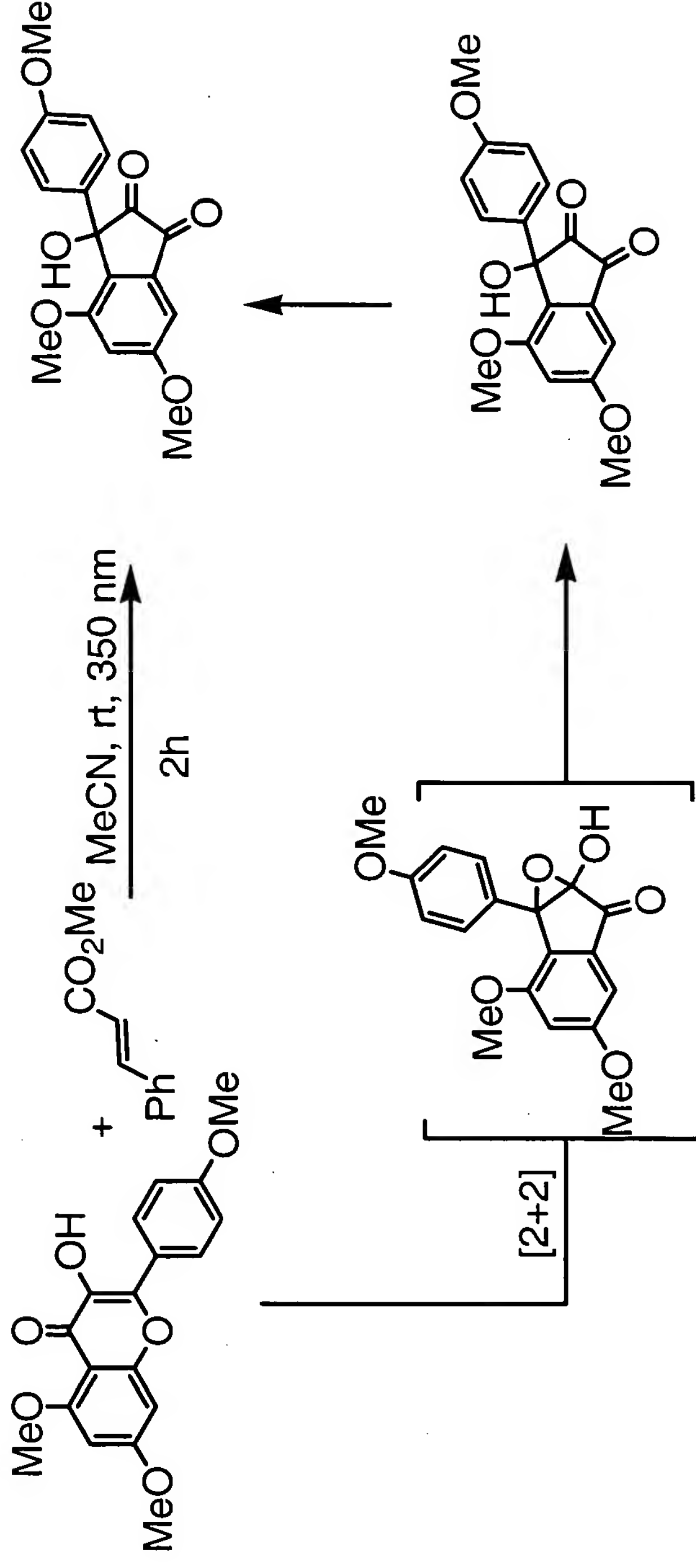
III) Preliminary result

B) Synthesis of a trisubstituted 3-hydroxyflavone



III) Preliminary result

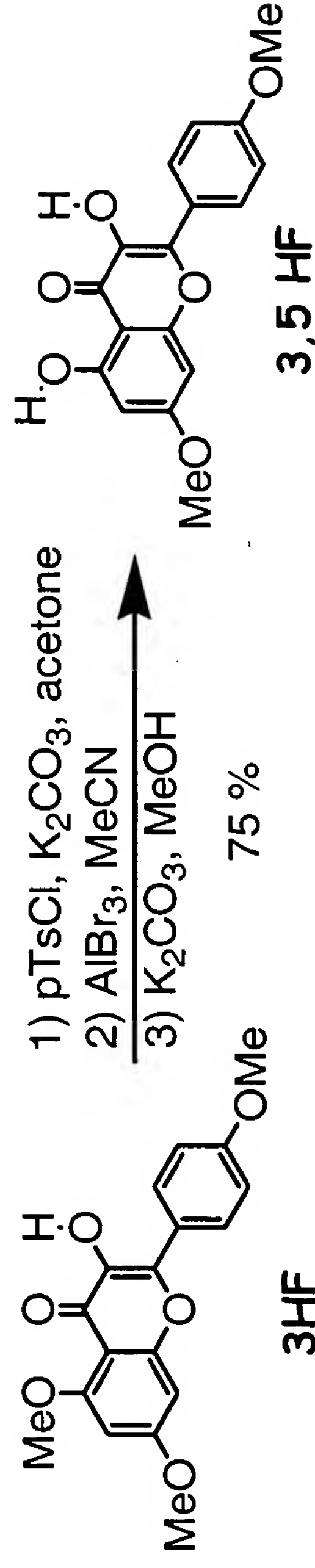
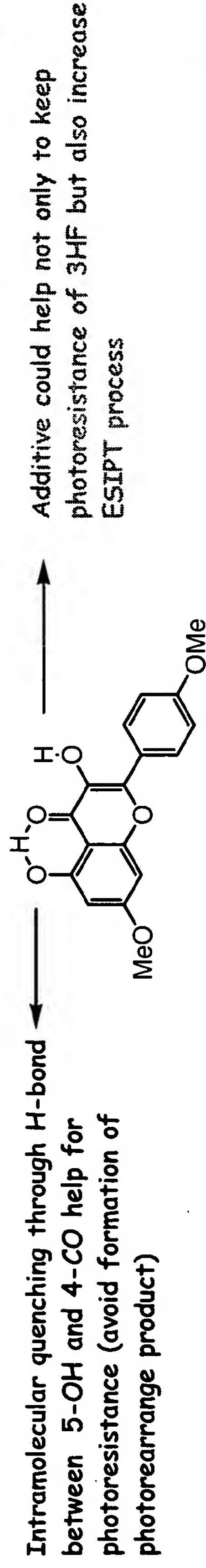
C) Attempted cycloaddition using trimethoxy hydroxyflavone



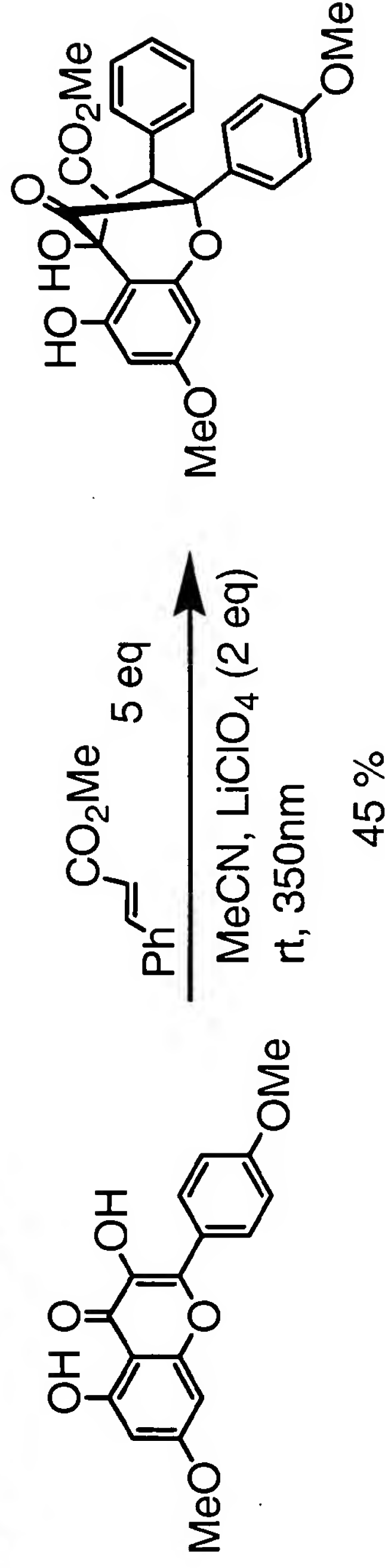
⇒ Several conditions (254 and 350 nm, solvent (MeCN, MeOH) and dipolarophile have been screened but no cycloadduct has been observed in initial experiments

III) Preliminary result

D) Substrate modifications and early results



Preliminary results (proposed regioselectivity)



IV) Summary

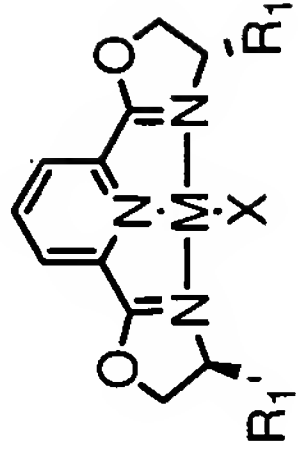
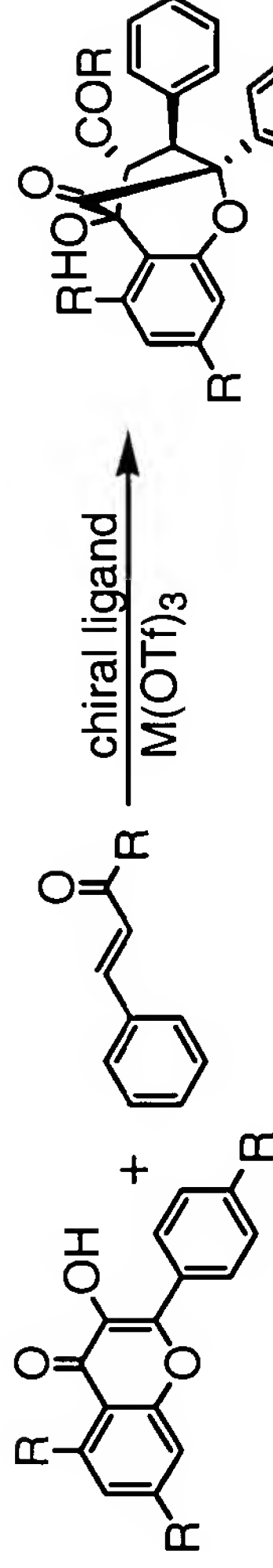
This poster outlines:

A plan towards the total synthesis of rocaglamide and related analogues

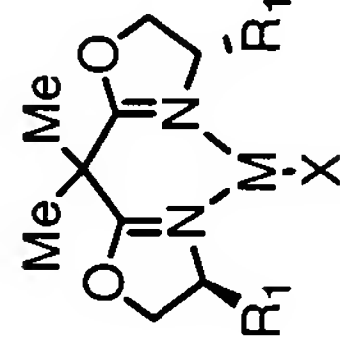
⇒ Formation of a 3HF pyrylium species will be promoted *via* a proton transfer reaction

⇒ Trapping of the dipole by cinnamic derivatives through a [3+2] cycloaddition

- Future plans include development of an asymmetric variant of the dipolar Cycloaddition using chiral lewis acid



Chiral ligand



R_1 : Ph, *i*-Pr, *t*-Bu

R_1' : Ph, *i*-Pr, *t*-Bu